REMARKS

This is a simultaneous amendment with request for continued examination filed together with a "Petition to Revive an Abandoned Application" in accordance with M.P.E.P. 711.03 (c). In addition, some additional comparative experimental evidence is filed under 37 C.F.R. 1.132 in an accompanying second Declaration to overcome rejections under 35 U.S.C. 103 (a).

I. NEW CLAIMS 47 AND 48

New dependent claims 47 and 48 have been added, which limit the particle size of the bioactive glass to less than or equal to 10 microns.

These new dependent claims have been added because the patentability of the combined subject matter of claims 36 and 47 and of claims 41 and 48 is supported by the experimental evidence in a new second Declaration showing unexpected improvements for the smaller bioactive glass particle sizes and also by the experimental evidence provided in the previously filed Declaration.

On the other hand, the independent claims have not been limited to a bioactive glass particulate with particle sizes less than 10 microns (5^{th} paragraph, page 4, of the specification) and argumentation to overcome the case of *prima facie* obviousness of the independent claims in the final Office Action dated December 20, 2007 are presented herein below.

Favorable allowance of claims 36 to 48 is respectfully solicited.

II. CANCELED CLAIMS

Claims 25 to 28 were rejected as obvious under 35 U.S.C. 103 (a) over Shimono, et al, (US 5,290,544), in view of Greenspan (WO 98/11853).

Claims 29 to 35 were rejected as obvious under 35 U.S. C. 103 (a) over Shimono, et al, (US 5,290,544), in view of Greenspan (WO 98/11853), and further over the technical articles of Yamanaka, et al; Wu, et al; and Wang, et al.

These rejections have been obviated, because of the cancellation of claims 25 to 35. Furthermore no independent claims have been added that contain the same limitations as claims 25 and 29.

III. CLAIMS 36 TO 46

Claims 36 to 46 were rejected as obvious under 35 U.S.C. 103 (a) over Shimono, et al, (US 5,290,544), in view of Greenspan (WO 98/11853), and further in view of Yli-Urpo, et al, (US 5,762,950).

A. Prima Facie Case

Independent **method** claim 36 covers a method of preserving a cosmetic preparation (in the form of an aqueous liquid or in some other form such as solid powder) in which from 0.1 to 25 wt. % of a bioactive glass particulate with particle sizes less than 1 mm, which comprises calcium and phosphorous in relative amounts such that a hydroxyapatite layer is formed on the particles in contact with an aqueous media, whereby antimicrobial action is provided.

Independent **composition** claim 41 covers a cosmetic preparation containing from 0.1 to 25 wt. % of a bioactive glass particulate with particle sizes less than 1 mm, which comprises calcium and phosphorous in relative amounts such that a hydroxyapatite layer is formed on the particles in contact with an aqueous media.

Thus the method protects the cosmetic composition against microbes that require water to survive and grow because, when, water is present, the bioactive glass particulate with the aforesaid particle size and composition forms a hydroxyapatite coating on the particles and thus acts to inhibit or prevent growth of the microbes. The cosmetic compositions containing the bioactive glass with the aforesaid particle size and composition are protected against such microbes because if it contacts water or contains water it will act to inhibit or prevent growth of the microbes.

1. Content and Scope of the Prior Art

Page 16 of the final Office Action states that Shimono teaches a "bioactive glass" and that Shimono teaches a glass particulate with the same particle size and ingredients as the bioactive glass of claims 36 to 46. It is respectfully submitted that these statements of fact are not accurate and are misleading.

Shimono discloses an antibacterial glass particulate containing silver cations, copper cations and/or zinc cations as the active antibacterial ingredient (column 1, lines 55; claim 1). The remaining glass particle matrix, which is disclosed by Shimono and used to contain the silver ions, copper ions and/or

zinc ions so that they can protect the cosmetic composition, is **bio-inactive** in the case of the glass compositions disclosed in Shimono. Also the glass compositions disclosed in Shimono have no antibacterial action without their toxic metal cations. Further Shimono does not disclose or suggest that the phosphate glass that is used to contain the metal cations would have any antibacterial action.

The term "bio**active** glass" has a special significance in the art. US 5,076,916 defines "bioactive glass" in their "Description of the Prior Art" in the BACKGROUND SECTION of their patent. This definition is also provided on page 2, lines 5 to 8, of applicants' originally filed specification. According to this and other references such as the article "Bioceramics: From Concept to Clinic" a "bioactive glass" is a **non-toxic glass** that will form an interfacial bond with tissue when it is implanted in the body. The glass particulates of Shimono contains toxic metal cations and are **not** bioactive glass because they do not form the interfacial bond since they do not have the correct ingredients.

US 5,076,916 also teaches that three key ingredients are required in bioactive glass: SiO_2, CaO and P_2O_5 (they are phosphate glass, not soda lime glass) and that the relative amounts of CaO and P_2O_5 are limited in order to form that hydroxyapatite layer that is necessary to form the interfacial bond between the bioactive glass and the tissue. The reference teaches a molar ratio of CaO to P_2O_5 of about five is necessary. Also the disclosures in the present application are similar (see the last full paragraph on page 3 of the specification).

The phosphate glass particulates disclosed and claimed (claims 4 and 6)

in Shimono do not have a sufficiently great molar ratio of CaO to P_2O_5 to be considered a bioactive glass particulate. Examples 2 and 4 of Shimono have molar ratios of CaO to P_2O_5 that are less than 1.

Furthermore the glass of examples 2 and 4 of Shimono do not include any SiO_2, which is also important for formation of a hydroxyapatite layer as described in the BACKGROUND SECTION of US 5,076,916.

Thus Shimino indeed discloses an antibacterial glass particulate, but not a bioactive glass particulate with antibacterial action.

Greenspan does disclose a bioactive glass composition with the right amounts of SiO_2, CaO, and P_2O_5. Greenspan teaches a composition containing a combination of the bioactive glass and an antibiotic, e.g. gentamicin or chlortetracycline, which is used to accelerate the healing of wounds, such as battlefield wounds. A method of use of the composition with skin grafts is also disclosed. Greenspan teaches that the precipitation of calcium and phosphorous in the blood and would causes formation of layer including collagen, fibrin and fibronectin as well as the calcium and phosphorous to stabilize the wound on page 12, last five lines.

However Greenspan does not disclose or suggest that their bioactive glass composition would be useful in preserving cosmetic compositions. Greenspan does not disclose cosmetic compositions. This WO reference does not teach any methods of preserving cosmetic compositions from antimicrobial action of any kind.

Greenspan teaches that control of infection is of critical importance in

healing a wound in the paragraph running from page 3 to page 4, because **bacteria** may contaminate the wound. Greenspan teaches that including **an antibiotic** with the bioactive glass is an essential requirement of their invention in the summary in the first paragraph on page 9 and in claim 1 of Greenspan. However even those who are **not** skilled in the art know that the purpose of applying a topical anti**biotic** is to kill bacteria and microbes generally.

There is no teaching in Greenspan that the bioactive glass composition disclosed in that reference has **by itself** antimicrobial action. Greenspan clearly discloses that their composition that includes the topical antibiotic and the bioactive glass speeds the healing of wounds (page 10).

More relevant teaching appears on pages 12 and 13 of Greenspan. Regarding the bioactive glass particulate Greenspan teaches that it functions to create the conditions that permit the antibiotic to be effective by activating various biochemical systems in the wound on page 12, lines 11 to 16. But a more effectively functioning antibiotic is a substance that more effectively kills bacteria. Thus the reference never teaches that the bioactive glass itself would be helpful in treating infections by killing bacteria itself.

Greenspan would lead one skilled in the arts **away** from including only bioactive glass itself without the antibiotic in a cosmetic composition to protect the cosmetic composition from bacterial or microbial action. One skilled in the art would assume that the bioactive glass is included to stabilize the wound by causing coagulation and producing a layer including collagen and fibrin and that it is the antibiotic, not the bioactive glass, that kills the bacteria or microbes.

At the very least one skilled in the art would assume that any antimicrobial action provided by the bioactive glass itself would be too ineffective and that the antibiotic is necessary to provide the required antimicrobial effectiveness.

The applicants' method claim 36 above does not claim a method in which a cosmetic composition comprising bioactive glass contacts with water to provide antimicrobial action. Instead applicants' claim 36 covers a method that includes adding the bioactive glass itself to the composition so that on contact of the bioactive glass with water (which is necessary for the microbe survival) antimicrobial action is provided by the bioactive glass (not the antibiotic).

Furthermore Greenspan does **not** teach that bioactive glass itself will form a hydroxyapatite layer on contact with water and thus provide antimicrobial action *without the presence of the antibiotic* which results from formation of the hydroxyapatite layer. Greenspan does not mention hydroxyapatite.

Yli-Urpo discloses implants and oral formulations for delivery of a bioactive compound, such as a medicine, containing hydroxyapatite and bioactive glass or compositions (column 1, lines 34 to 42). The bioactive glass or ceramic compositions containing mixtures of SiO_2, alkali cations, CaO, P_2O_5, and other oxide ingredients do not cause an inflammation reaction when implanted in the body (column 1, lines 22 to 30). That is the reason that they are used for implants.

Yli-Urpo describes the effects of including the hydroxyapatite with the bioactive glass in column 3, lines 40 to 62, and also discloses that their delivery compositions containing hydroxyapatite and bioactive glass produce a system,

whose resorption rates and whose activity are controllable according to column 1, lines 45 to 55.

Yli-Urpo discloses examples of their delivery system and pharmaceutical compositions in columns 6 to 9. The experimental results solely concern release rates and dissolution rates of bioactive compounds.

However Yli-Urpo does **not** disclose or suggest that their hydroxyapatite and/or bioactive glass have a bacteriostatic effect. Furthermore there is no data presented regarding bacterial growth inhibition or prevention. There is no mention of any antimicrobial action whatsoever in this reference, which is solely concerned with the use of bioactive glass as an implant material that is compatible with living tissue.

In summary the disclosures of secondary references Greenspan and Yli-Urpo do not teach or provide evidence that the disclosed bioactive glass itself without other compounds has antimicrobial action. This element is missing from the cited prior art references.

2. Lack of Rationale for an Obviousness Rejection

In regard to the rationale provided on page 16 to 17 it should be noted that the composition of Greenspan that provides a bacteriostatic effect contains an antibiotic, which is of course expected to provide an antibacterial action. There is no teaching that the bioactive glass alone without the antibiotic provides effective antibacterial action.

However applicants' claimed method, for example, is limited to providing

antibacterial action via the bioactive glass. The claim wording of claim 36 does not state that any other substance is added to assist in providing antimicrobial action. The same reasoning applies to the improvement claim 41.

Yli-Urpo does disclose implants that include bioactive glass compositions and hydroyapatite but there is no teaching that these systems have antibacterial action, only teaching that they are compatible with living tissue and do not cause inflammation when implanted.

Yli-Urpo discloses no subject matter that would be helpful for protecting cosmetic compositions from microbial contamination and growth.

Even if the secondary references teach the applicants' preferred bioactive glass compositions they do not teach that these bioactive glass compositions have antimicrobial action by themselves without other organic compounds (antibiotics). At the very least they do not suggest that they would be effective in providing sufficient protection for cosmetic compositions from bacterial contamination.

Although obviousness does not require absolute predictability, at least some degree of predictability is required. See M.P.E.P. 2143.03 and ***In re Rinehart***, 189 U.S.P.Q. 143(C.C.P.A. 1976). Here in the case of the instant claims 36 to 46 there is no reason to expect from the secondary references, Greenspan and Yli-Urpo, that addition of from 0.1 to 25 wt. % of the bioactive glass particulate according to claims 36 and 41 to a cosmetic composition would provide antibacterial action in the presence of water that is sufficient to protect the cosmetic composition from bacterial contamination. Yli-Urpo does not even

mention bacterial contamination and Greenspan does not clearly teach that the bioactive glass compositions disclosed in that reference would have bactericidal action without the presence of an antibiotic that is included in their composition. Otherwise what would be the purpose of including the antibiotic?

It is well established that the prior art must disclose or make obvious all the limitations of a claimed invention for a valid obviousness rejection under 35 U.S.C. 103 (a) (see M.P.E.P. 2143.03) In the case of the present application the prior art references do not teach or make it obvious that the bioactive glass has antimicrobial action without the presence of other ingredients, namely the antibiotic of Greenspan.

Many cosmetic compositions contain ingredients that are essentially nourishing food for bacteria. It is not uncommon to provide fatty alcohols and fatty esters in cosmetic compositions. Some cosmetic compositions contain protein hydrolyzates and vitamins. Thus bacteria find ingredients in cosmetic compositions that are easily attacked and supply nourishment for growth and multiplication.

Shimono discloses glass particulates, which are not bioactive glass and which contain **toxic** cations that are delivered to their cosmetic compositions on contact with water. Even if it is known that a bioactive glass particulate provides some antibacterial action under some circumstances, one could not conclude that the bioactive glass particulate that delivers **non-toxic** cations, such as Na+ cations, which are compatible with human tissue, would provide sufficient anti-

bacterial action to provide a cosmetic composition with sufficient protection from anti-bacterial action.

If an obviousness rejection is proposed based on a combination of the disclosures of Shimono and another reference that teaches a bioactive glass composition that has bactericidal action in some other type of field, then this supposed obviousness rejection must be based on a replacement of the bactericidal particulate of Shimono with the bioactive glass particulate of the other reference. However the principle of operation of the protection from bactericidal contamination is entirely different because in the case of Shimono the antibacterial action is based on delivery of toxic metal cations from an inert glass matrix, while in the case of the bioactive glass the bactericidal action is based on the changes in pH of the aqueous medium and delivery of non-toxic cations that result in formation of the hydroxyapatite layer when the bioactive glass has a sufficiently high molar ratio of CaO to P_2O_5. One might expect that the toxic cations would be more effective in eliminating bacterial contamination but the biocompatible bioactive glass would not.

Thus the proposed modification of Shimono to arrive at the claimed invention is not valid under 35 U.S.C. 103 (a) because the modification would change the basic principle of operation of the prior art glass particulate. For example M.P.E.P. 2143.01 states as follows:

> **"If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (Claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers**

inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. Patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." (270 F.2d at 813, 123 USPQ at 352.)."

In the case of the present invention substantial modification of the disclosures in the primary reference is required in order to arrive at an entirely different glass particulate composition without toxic cations in which the glass itself provides the antimicrobial action via a different mechanism of action. Instead of feeding the microbes toxic cations biocompatible materials are used, which is especially desirable in a cosmetic composition that is applied to skin and/or hair in use. The antimicrobial action of the bioactive glass of the applicants is based on a change in pH on contact with water that produces a hydroxyapatite layer on the bioactive glass.

For the foregoing reasons it is respectfully submitted that the combined disclosures of Shimono, et al; Greenspan; and Yli-Urpo, et al; do not establish a case of *prima facie* obviousness of the above pending claims.

2. Evidence of Unexpected Results

In addition applicant has already presented comparative evidence in a Declaration that shows that unexpectedly better antibacterial action is provided

by bioactive glass of the claimed compositions with the smaller particle size. This evidence supports the disclosure in the fifth full paragraph on page 4 of the applicants' disclosure that states that the smaller the average particle size the higher is the bactericidal activity.

The first comparative evidence was filed in a Declaration under 37 C.F.R. 1.132 dated November 11, 2004, which is of record. The evidence showed 1 % aqueous solutions of bioactive glass particulates containing 45 wt. % SiO_2, 24 wt. % Na_2O, 24.50 wt. % CaO, and 6.00 wt. % P_2O_5 with particle sizes from 1.6 to 9 microns were used to prepare 1 % aqueous preparations had pH values from 10.56 to 11.23, which were sufficiently alkaline to form hydroxyapatite. After innoculation with a cocktail of five different common bacteria three species were effectively completely killed after 2 days while one species required a week to eliminate completely and another required several weeks to be eliminated. Results for the 2 and 4 micron bioactive glass particulates showed that the 2 micron particulate was unexpectedly better at eliminating the two difficult-to-kill species.

An additional Declaration with new comparative evidence that clearly shows the importance of particle size (D_{50}) of 10 μm and under and unexpectedly better antimicrobial results using bioactive glass particulates with the smaller particle sizes has been prepared and filed along with the present amendment. Bioactive glass particulates according to the present invention were prepared with particle sizes (D_{50}) of 4 μm, 10 μm, 30 μm, and with a coarse bioactive glass particulate with grain sizes between 150 and 600 μm.

Generally the bioactive glass particulates with the smaller particle sizes are more effective against various microbes. Unexpectedly the coarse bioactive glass particulates are ineffective against a majority of the five tested microorganisms, even the common *E. Coli.* The results are especially dramatic for *Candida albicans* and *Aspergillus niger*. The measured microorganism counts a significant improvement for bioactive glass particulates with particle sizes of about 4 microns in comparison to the bioactive glass particulates with a particle size of about 10 microns.

These results support patentability of the combined subject matter of claims 36 and 47 and of claims 41 and 48, which limit the claimed improvements to bioactive glass particulates that have particle sizes of 10 microns or less. These comparative results clearly establish the critical nature of the particle size parameter and overcome any case of *prima facie* obviousness of claims 47 and 48.

These objective experimental results that show non-obviousness of the claimed subject matter must be considered and should be effective in overcoming any case of *prima facie* obviousness based on the prior art of record. See M.P.E.P. 716.

The second Declaration accompanying this amendment is unsigned but a signed copy will be provided as soon as possible.

For the foregoing reasons withdrawal of the rejection of claims 36 to 46 as obvious under 35 U.S.C. 103 (a) over Shimono, et al, (US 5,290,544), in view of Greenspan (WO 98/11853), and further in view of Yli-Urpo, et al, (US

5,762,950) is respectfully requested.

In addition it is respectfully submitted that the new claims 47 and 48 should not be rejected under the aforesaid grounds for obviousness under 35 U.S.C. 103 (a).

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

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